Short, novel syntheses of lactones and furans of marine origin

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RESEARCH REPORT

SHORT, NOVEL SYNTHESES OF LACTONES AND FURANS OF MARINE ORIGIN (*)(**)

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Summary — New regio- and diastereoselective processes have been developed in which furanolates are efficiently transformed into substituted γ-lactones and furans. The power of the methodology is illustrated by the syntheses of siphonodictidine, pleraplysillin-2, cavernosine, bromobeckerelide, acetoxyfimbrolide, and related marine natural products.

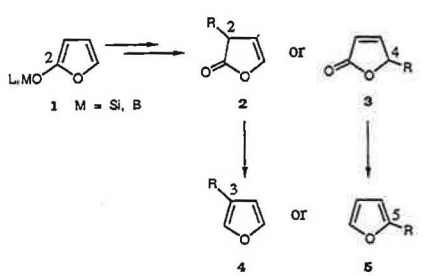
INTRODUCTION

A significant portion of natural products of marine origin are γ-lactones and furans[1]. Many of them are endowed with a wide range of biological activity. Unfortunately, such interesting molecules are often only available in tiny amounts. Consequently, there is a need to develop synthetic methods that are cheap, operationally simple and which deliver the required product in good yield.

The point of departure for attacking this problem was the idea that a suitable 2-furanolate derivative (**1**) would act as a masked equivalent of both the butenolide (**2** and **3**) and furan (**4** and **5**) entities. By an appropriate choice of the ligand M the reactivity of **1** could be modulated to provide controlled access to 2- or 4-substituted butenolides (**2** and **3**) by means of two reaction types, alkylation and aldolization. Thereafter, reduction, where necessary, to the related 3- and 5-substituted furans (**4** and **5**), followed by further chemical modification would furnish the desired target molecules (scheme 1).

At the outset, it was already known that 2-(trimethylsiloxy)furan, **9**, reacted with a variety of electrophiles, *e.g.* aldehydes[2],ketones[2], acetals[3], ortho-esters[3], and lead tetraacetate[4], at the C5 position. However, despite these good omens, the synthetic potential of **9** had not been exploited.

SCHEME 1

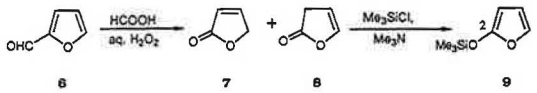


ALKYLATIONS

No instance of alkylation of **9** had been reported except for Michael addition to α,β-unsaturated ketones[5]. However **9**, or an equivalent, should behave like silyl enol ethers[6] and react with alkyl halides on catalysis with Lewis acids. The examples which follow confirm this expectation.

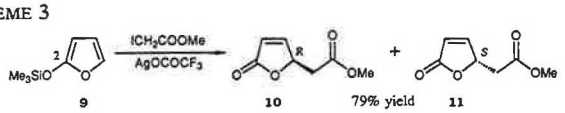
The first target selected is the simplest. The butenolide **10** having the *S* configuration was isolated from the sponge *Xestospongia* sp. and found to be active against P388 murine leuchaemia cells[7]. Its absolute configuration was deduced by a multi-step synthesis of its antipode[8]. In contrast, the obvious alkylation of 2-(trimethylsiloxy)furan, **9**, with methyl α-iodoacetate would yield the racemic butenolide (**10** and **11**) directly. First, the requisite 2-(trimethylsiloxy)furan, **9**, was procured by Baeyer-Villiger oxidation of the readily available furfural **6**[9]. The intermediate 2-furanones (**7** and **8**), on treatment with trimethylsilyl chloride gave **9** (scheme 2).

SCHEME 2



Secondly, external activation of the halide with silver trifluoroacetate was found to be necessary to ensure reaction with **9**. Alkylation was completely regioselective and gave **10** and **11** in 79% yield[10] (scheme 3). Alkylation also worked well with 2-butenyl bromide and even *n*-nonyl iodide giving the non-allylically rearranged, and primary alkyl products in high yields. Mechanistically the silver salt complexes with the «soft» halide to engender the formation of a «soft» carbocation which is attacked in an S_N2 process by the most nucleophilic position of the furan ring[11]. The formation of the racemate is not a

SCHEME 3



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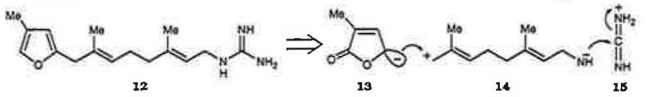
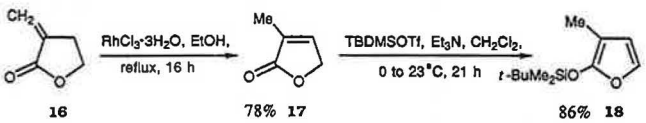
SCHEME 4



disability as the enantiomers (**10** and **11**) are easily resolvable by chromatography over cellulose triacetate[12].

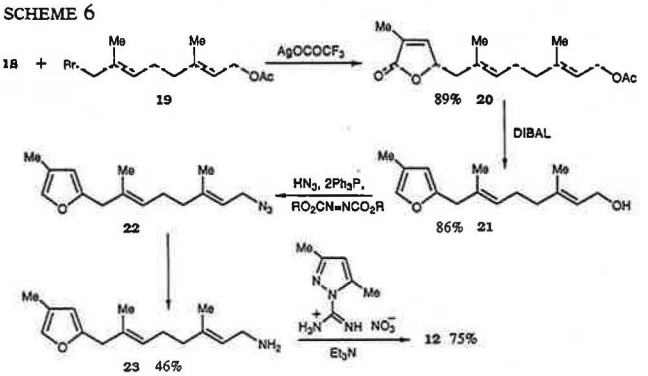
The aforementioned alkylation method can also be used for synthesizing siphonodictidine, **12**, pleraplysillin-2, **24**, and the structurally related furanosesquiterpene **25**. Siphonodictidine, **12** was isolated from an Indo-Pacific sponge *Siphonodictyon coralliphagum* which invades and kills coral[13]. Anti-microbial properties were reported for **12**. Consideration of the disconnections reveal that the chemistry to be accomplished consists in the coupling of a localized furan anion (**13**) with an allylic cation synthon (**14**) at one end, while an amidine cation (**15**) needs to be attached to an amide ion at the other terminus of **14** (scheme 4). Reduction to practice, however, requires the reagents 2-*t*-butyldimethylsiloxy-3-methylfuran, **18**, and bromogeranyl acetate, **19**. First **18** had to be prepared from 3-methylidene-2-furanone, **16**[14]. Isomerization to 3-methyl-2-furanone, **17**, was accomplished with rhodium chloride. Thereafter, treatment with *t*-butyldimethylsilyl trifluoromethanesulphonate gave **18** (scheme 5). Coupling of **18** with bromo-

SCHEME 5



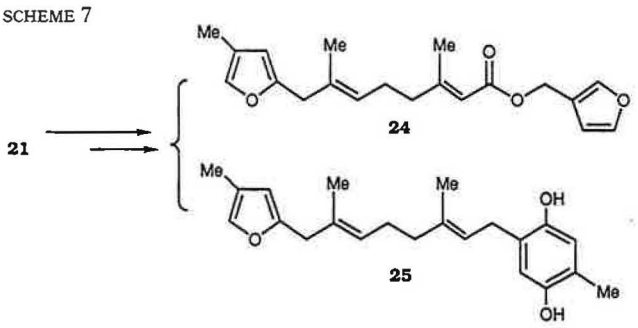
geranyl acetate, **19**, a known compound[15], was effected, as before, in the presence of silver trifluoroacetate (scheme 6)[16]. The butenolide acetate **20** was obtained in 89% yield, and then reduced with diisobutylaluminium hydride (DIBAL) to the furanoalcohol **21**. Conversion of **21** to the primary amino function was effected by the Mitsunobu reaction[17] with hydrazoic acid, but conducted with a two-fold excess of triphenylphosphine[18]. Under these conditions, the intermediate azide (**22**) lost nitrogen to yield the non-isolated Staudinger intermediate[19] which on hydrolysis gave the primary amine **23**. Finally, reaction of **23** with 3,5-dimethylpyrazole-1-carboxamidine nitrate, in the presence of base[20],

SCHEME 6



gave siphonodictidine, **12**. Pleraplysillin-2, **24**, a constituent found in the Mediterranean sponge *Pleraplysilla spinifera*[21], and related furanosesquiterpenes (*e.g.* **25**) isolated from Australian soft corals[22] are accessible from the key intermediate alcohol **12** (scheme 7).

SCHEME 7

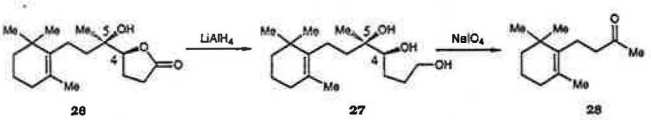


ALDOLIZATIONS

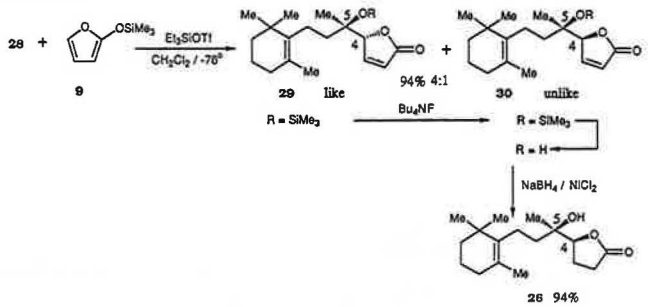
Apart from alkylation, aldolization is one of the fundamental bond-forming reactions in organic chemistry. The furan derivative **9** should behave as a typical dienol silyl ether. Early signs of such reaction were favourable[3]. Confirmation is provided by the following example.

Cavernosine, **26**, was isolated from the marine sponge *Fasciospongia cavernosa* and is toxic to potentially predatory fish[23]. Its structure and the unlike configuration at the C4C5 atoms were elucidated by reduction to the triol **27** and by subsequent oxidative cleavage to dihydro-β-ionone, **28** (scheme 8). It was immediately obvious that synthesis could be economically brought about by aldol condensation of dihydro-β-ionone, **28**, with 2-(trimethylsiloxy)-furan, **9** (scheme 9). Many typical Lewis-acid catalysts were tried, but the most effective turned out to be triethylsilyl triflate (Et_3SiOTf)[24]. Condensation occurred exclusively at the C5 position of **9**. In all cases, the ratio of like to unlike butenolides (**29** and **30**) remained essentially the same, which was always biased towards the like or unwanted configuration.

SCHEME 8



SCHEME 9

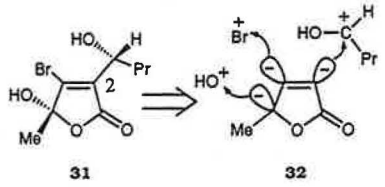


However, treatment of the kinetic product mixture with *n*-tetrabutylammonium fluoride followed by hydrolysis resulted in equilibration by prototropy to the more stable diastereomer of unlike figuration (**30**). Subsequent reduction of **30** with sodium borohydride and nickel chloride gave cavernosine, **26**.

In 1977 an interesting family of highly substituted, halogenated butenolides, some possessing antimicrobial properties, was discovered. Typical members are bromobeckerelide, **31**, the major constituent of *Beckerella subcostatum* which was collected off Kozu Island[25] and (*Z*)-acetoxyfimbrolide, **48**, isolated from a sample of *Delisea fimbriata* which was collected near Sydney[26].

Analysis of the disconnections of **31** reveals the chemistry needed for synthesis, namely three electrophilic operations, hydroxylation, bromination and aldolization at the appropriate anionic centres on the methylbutenolide framework **32** (scheme 10).

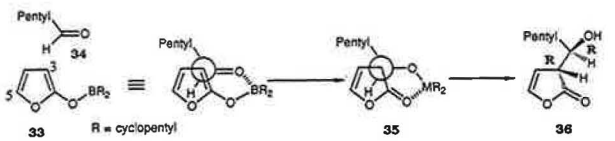
SCHEME 10



31 **32**

The critical process of regioselective aldolization was secured thanks to the agency of a boron substituent. In an independent experiment[27], biscyclopentylboron 2-furanolate, **33**, was allowed to react with capronaldehyde, **34** (scheme 11). Aldolization occurred to give the 2-(1'-hydroxyhexyl)-butenolide, **36**, in 98% yield. This regioselective result springs from the complexation of the aldehyde molecule with the boron substituent, thereby favouring bond formation at the C3 position of the furan ring (**35** → **36**). With this information in hand, the synthesis of bromobeckerelide was undertaken

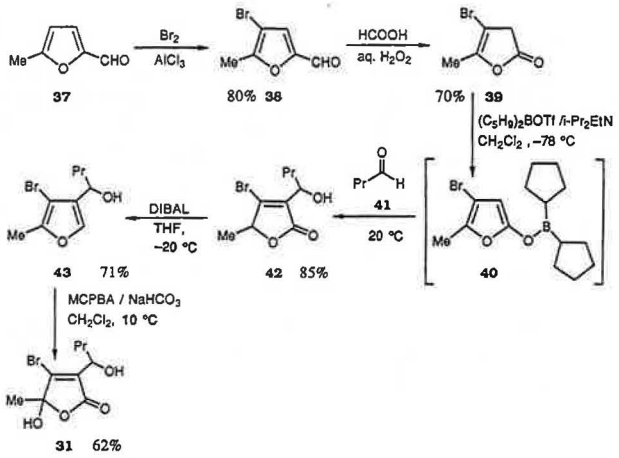
SCHEME 11



33 R = cyclopentyl **35** **36**

starting from 5-methylfurfural, **37** (scheme 12)[28]. Bromination occurred in good yield, under Lewis-acid catalysis, at the expected more nucleophilic C4 position. Baeyer-Villiger oxidation of the resulting bromofurfural **38** afforded the 4-bromo-5-methyl-2(3*H*)-furanone, **39**, which was converted *in situ* to the boron furanolate **40**. Addition of butanal, **41**, provided the expected 3-(1'-hydroxybutyl)-2-furanone, **42**. Although the latter, in principle could be hydroxylated directly with peracid, prior reduction with DIBAL to the furan-alcohol **43**, followed by double electrophilic oxidation with *m*-chloroperbenzoic acid (MCPBA) was effected instead. The

SCHEME 12

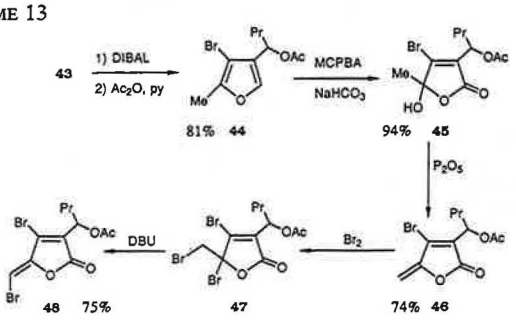


37 80% **38** 70% **39** **43** 71% **42** 85% **40** **31** 62%

racemic bromobeckerelides, **31**, comprising the diastereomers in a 1:1 ratio, were obtained in five steps in an overall yield of 21% and displayed an NMR spectrum identical to that of the authentic material.

Extension of this method also yielded (*Z*)-acetoxyfimbrolide, **48**[29]. Acetylation of the furan-alcohol **43** to **44**, followed by double hydroxylation, gave the hydroxybutenolide **45** (scheme 13). Dehydration with phosphorus pentoxide to the γ-methylidene derivative **46**, followed by bromination (**47**) and dehydrobromination gave only the (*Z*)-acetoxyfimbrolide **48**.

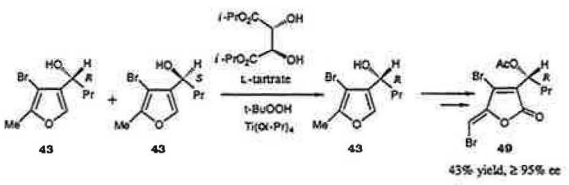
SCHEME 13



43 **44** 81% **45** 94% **46** 74% **47** **48** 75%

Lastly, in a wasteful, but convenient procedure, the racemic furan-alcohol **43** was subjected to asymmetric epoxidation using L-tartrate as the chiral director according to Sharpless[30] (scheme 14). Satisfactory kinetic resolution was obtained. The furan-alcohol of the *R* configuration survived these conditions and was subsequently converted by the previously mentioned sequence to furnish enantiomerically pure (*Z*)-acetoxyfimbrolide of the *R* configuration, **49**, which was identical to the natural material[29].

SCHEME 14



43 **43** **43** **49**

43% yield, ≥ 95% ee

CONCLUSION

Although not discussed here for reasons of relevance, the furanolate methodology has been used for synthesizing natural products of similar structural type, but of terrestrial origin[11,14]. The present examples amply demonstrate the utility and scope of the furanolate reagents. Moreover, the starting materials are commonly available; the experiments are easy to perform and give substantial amounts of the desired products in just a few steps.

It is a pleasure to thank my co-workers G. Bernardinelli, J. Boukouvalas, P. Huang, D. Jaggi, J.C. Rossier and A. Sledeski for their contributions.

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